Impact of Venous Thromboembolism on Mortality of Elderly Medicare Patients with Stage III Colon Cancer

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify the prevalence of adjuvant chemotherapy utilization in elderly patients with stage III colon cancer.
2. Discuss the prevalence and impact of venous thromboembolism in elderly patients with stage III colon cancer.
3. Identify potential for development of a clinical trial to study the clinical benefit and impact on cancer-specific and all-cause mortality of thromboprophylaxis during adjuvant chemotherapy in elderly patients with stage III colon cancer.

CME

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ABSTRACT

Background. The improvement in survival rates for patients with colon cancer has shifted the focus from examining cancer-specific mortality to exploring all-cause mortality. Adverse events such as venous thromboembolism (VTE) affect overall survival times and the net clinical benefit of cancer management strategies.

Methods. This retrospective study used Surveillance, Epidemiology and End Results (SEER) Medicare data to examine VTE incidence and mortality rates for elderly

patients with stage III colon cancer who were diagnosed in 2004 or 2005 and followed through 2007. The impact of VTE on mortality was estimated using multivariable Cox proportional hazards regression.

Results. In all, 20.7% of 4,985 elderly patients with stage III colon cancer had clinically diagnosed VTE following diagnosis. All-cause mortality risk was higher for patients with a VTE diagnosis (hazard ratio [HR]: 1.15, 95% confidence interval [CI]: 1.04–1.27), greater comorbidity bur-

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den, more advanced tumor depth and nodal involvement within stage III, advanced age, and male sex; the risk was lower for patients treated with chemotherapy. VTE was associated with higher mortality hazards (HR: 1.41, 95% CI: 1.21–1.64) for patients treated with adjuvant chemotherapy but not for untreated patients.

Conclusions. A new diagnosis of VTE significantly re-

duced survival rates for elderly patients with stage III colon cancer and further reduced survival rates for patients treated with chemotherapy. Improved prevention and management of VTE for elderly patients with stage III colon cancer who are at risk for VTE is warranted, particularly for patients treated with chemotherapy. *The Oncologist* 2012;17:1191–1197

INTRODUCTION

Venous thromboembolism (VTE), which includes pulmonary embolism (PE) and deep vein thrombosis, is both a marker of cancer risk and an outcome that is more likely to occur after a cancer diagnosis. The occurrence of thromboembolism can precede the diagnosis of malignant disease by months or years [1–3] or can occur subsequent to cancer diagnosis [4, 5]. Patients with cancer have an inherently increased risk of developing VTE [6–9] because of the presence of major risk factors, including cancer-associated hypercoagulable state, vessel wall damage and vessel stasis from direct compression, advanced age, surgical procedures, prolonged immobilization, frequent hospitalization, use of erythropoietic stimulating agents, and the frequent use of indwelling vascular catheters and chemotherapeutic regimens.

VTE incidence is particularly high for certain types of cancers, including colon cancer [2, 10–11]. The incidence of VTE in patients with colorectal cancer is highest during the first 6 months after diagnosis and decreases over time [4, 12–13]. VTE incidence varies across cancer stages; the incidence of VTE in colorectal cancer is largely confined to patients with advanced disease [2, 4, 12, 14]. A high predisposition for the development of VTE exists for patients with colon cancer with the following principal risk factors: hospitalization, regional stage or metastatic disease, number of chronic comorbid conditions, systemic chemotherapy, prior VTE, African American race, and advanced age [2, 4, 15–18].

Although VTE is a preventable cause of death [19], it remains the leading cause of death in patients with overt malignancy [20], second only to the cancer diagnosis. VTE is the most common cause of 30-day mortality among patients with cancer who undergo surgery [21]. Compared with patients without cancer, patients with cancer have higher risk of recurrent VTE [22], bleeding on anticoagulation [22], and a 2- to 6-fold increased likelihood of dying after an acute event [12, 14, 23–26].

The presence of symptomatic VTE is different and often more severe for patients with cancer than for patients free from malignancy [23]. The risk of mortality associated with VTE remains a significant predictor of reduced survival in patients with malignancy [4, 14, 24–25], irrespective of stage of disease [14, 26]. Survival prognosis is less favorable for certain subpopulations, including African Americans, the elderly, and patients with recurrent VTE [27–29]. Patients who develop VTE have a higher probability of developing progression during treatment, suggesting that VTE may reflect the presence of a biologically more aggressive cancer in these patients [4, 22].

Several studies have documented an increased risk of de-

veloping VTE for patients with cancer who are treated with certain cytotoxic chemotherapy regimens [27–29]. For patients with colon cancer who are treated with systemic chemotherapy, there is an additional 2.2-fold increase in the risk of VTE compared with patients who have not received chemotherapy treatment [16, 30–31]. In a retrospective study, patients with colorectal cancer who were treated with chemotherapeutic regimens had an annual VTE incidence of 10.9% [32].

A recent survey reported that only 50% of surgical oncologists and 5% of medical oncologists routinely used VTE prophylaxis in their patients [33] and only 45% of hospitalized patients with cancer received any form of VTE prophylaxis [34, 35]. Postmortem reports also suggest that approximately 80% of cases of fatal PE occur in nonsurgical patients [36]. These reports and surveys indicate that there is gross underutilization of VTE prophylaxis regimens in patients with cancer, especially when hospitalized.

Because of the increased risk of cancer-associated VTE and its complications and its negative impact on survival, especially in patients receiving chemotherapy, there is a need for better evidence of the real-world impact of VTE among patients with colon cancer who receive adjuvant chemotherapy. Using the Surveillance, Epidemiology, and End Results (SEER) Medicare database, we estimated the impact of VTE on mortality for patients with stage III colon cancer.

METHODS

The SEER–Medicare linked dataset combines data from the SEER program, which collects patient-level information about incident cancer cases (including type of cancer and extent of disease) with administrative claims data from Medicare that contain comprehensive information about covered services used by enrollees in the United States. The resulting dataset provides sociodemographic, clinical, and mortality information, as well as health care utilization information for all Medicare enrollees diagnosed with cancer within 17 geographic regions representing approximately 26% of the U.S. population. The data for this study included 8,270 SEER patients diagnosed with incident stage III colon cancer in 2004 and 2005 and their associated claims from 2003 through 2007.

To minimize bias due to unobserved claims data, we included in the study only patients with complete Medicare coverage (i.e., with both Medicare Part A [hospital insurance] and Part B [medical insurance]) and excluded patients enrolled in a managed care plan 1 year prior to cancer diagnosis. We further excluded patients who were 65 years and younger at the time of cancer diagnosis because they lacked a full year of claims data

for the accurate ascertainment of baseline comorbidities. Finally, two patients who were diagnosed postmortem were excluded. The remaining 4,985 patients were followed up through December 2007. Subjects were censored from the study upon loss of complete Medicare coverage or upon enrollment in a managed care plan.

Statistical Analysis

All-cause mortality was the primary endpoint in this study. In contrast to disease-specific mortality, all-cause mortality is not affected by bias in classifying cause of death [37]. For each patient, a Charlson comorbidity index (CCI) score was calculated and a proxy for poor performance status was ascertained from claims in the year prior to cancer diagnosis. Poor performance status was indicated by hospitalization or use of oxygen, walking aid, or wheelchair. VTE incidence and adjuvant chemotherapy receipt were assessed from claims in the period following cancer diagnosis. The diagnosis of VTE was based on established diagnosis codes from the *International Classification of Diseases, Ninth Edition*.

The Pearson χ^2 and t tests were used to compare frequency distributions of categorical and continuous variables, respectively. Cox proportional hazards models were used to estimate the association of VTE following cancer diagnosis and mortality after controlling for receipt of chemotherapy, proxy for poor performance at baseline, CCI, substage of cancer disease, age, race/ethnicity, sex, and marital status. Similar proportional hazards models were conducted on subgroups stratified by whether or not patients received chemotherapy. The reported hazard ratio (HR) estimates reflect the relative hazards of death associated with each covariate in the model. Analyses were performed using SAS 9.2 (SAS Institute, Cary, NC) and $p < .05$ was considered statistically significant.

RESULTS

A total of 4,985 patients with stage III colon cancer were identified during the 2-year study period. The mean age in the study sample was 78 ± 7 years. Approximately 56% of patients were women and 82% were non-Hispanic white. Almost 60% of patients were diagnosed with substage IIIB colon cancer, whereas those with substage IIIA and substage IIIC cancer accounted for 11% and 30% of the total, respectively. The median follow-up time after stage III colon cancer diagnosis was 28 months (25 ± 14 months), during which 2,205 (44%) patients died. The median time from cancer diagnosis to first VTE diagnosis was 4 months. The unadjusted rate of VTE diagnosis was 9% at 3 months, 13% at 6 months, and 16% at 1 year after cancer diagnosis. Overall, 1,033 (21%) patients were clinically diagnosed with VTE any time during the follow-up period. Only 53.2% of all patients received adjuvant chemotherapy. As expected, the majority of the regimens were 5-fluorouracil/leucovorin/oxaliplatin and 5-fluorouracil/leucovorin/irinotecan.

Table 1 shows the distribution of sociodemographic and clinical characteristics by VTE diagnosis. The rate of VTE occurrence was higher in African Americans (26%, $p < .01$), urban residents (21%, $p = .01$), patients with prior VTE (51%,

$p < .01$), and patients with poor performance status (23%, $p = .03$). The rate of VTE occurrence had a nonlinear relationship with age, with a peak of 22% in 75- to 79-year old patients ($p = .03$). The rate of VTE significantly increased with the number of comorbidities, from 20% for patients with a CCI of 0 to 24% for patients with a CCI ≥ 2 ($p = .03$). Patients who received chemotherapy were diagnosed more frequently with VTE than those without chemotherapy treatment (24% vs. 17%; $p < .01$).

The mortality rate was higher for patients diagnosed with VTE (49%) than for patients without a VTE diagnosis (43%). Mortality rates increased with age, from a low of 27% for 66- to 69-year-old patients to a high of 65% for patients 85 years of age and older ($p < .01$). Mortality rates were higher for African American patients (47%, $p < .01$), patients who had a VTE episode during the year prior to cancer diagnosis (52%, $p = .02$), patients with an indication of poor performance status (57%, $p < .01$), patients with a CCI ≥ 2 (57%, $p < .01$), and patients with substage IIIC colon cancer (56%, $p < .01$). Mortality rates were lower for married patients (39%, $p < .01$) and patients treated with chemotherapy (30%, $p < .01$).

Multivariate Analyses

A Cox proportional hazards regression analysis estimated the association between being diagnosed with VTE any time following cancer diagnosis and the hazard of death after controlling for other patient and treatment factors. As shown in Table 2, VTE increased the hazard of death by 15% (HR: 1.15, 95% CI: 1.04–1.27). Other factors that significantly increased the risk of death were poor performance status (HR: 1.29, 95% CI: 1.17–1.43), CCI ≥ 2 (HR: 1.29, 95% CI: 1.15–1.45), male sex (HR: 1.15, 95% CI: 1.06–1.26), and age.

Compared with patients with substage IIIB colon cancer, patients with substage IIIA disease had a 42% lower hazard of death (HR: 0.58, 95% CI: 0.49–0.69), whereas patients with substage IIIC disease had a 72% higher hazard of death (HR: 1.72, 95% CI: 1.57–1.88). Patients who received chemotherapy had a 61% lower mortality hazard (HR: 0.39, 95% CI: 0.36–0.43).

Analysis by Chemotherapy Treatment

Chemotherapy receipt was associated with several patient characteristics and outcomes, which reflects the nonrandom treatment assignment that occurs in real-world practice. Patients treated with chemotherapy had significantly lower mortality rates and their median time from cancer diagnosis to death was more than 2.5 times higher compared with patients who did not receive chemotherapy.

Stratified Cox proportional hazards regressions examined the association between VTE and mortality separately for patients treated with chemotherapy. The results are reported in Figure 1. In treated patients, VTE incidence after cancer diagnosis increased the adjusted hazard of death by 41% (HR: 1.41, 95% CI: 1.21–1.64). However, after adjusting for covariates, there was no significant association between VTE and mortality among untreated patients.

Table 1. Distribution of demographic, comorbidity, and clinical patient characteristics by venous thromboembolism diagnosis

	Cohort, <i>n</i> (%)	Patients diagnosed with venous thromboembolism ^a		
		<i>n</i> (%)	Rate ^b	<i>p</i> -value ^c
Total	4,985	1,033		
Age				.03
66–74 years	1,716 (34.5)	376 (36.4)	21.9	
75–79 years	1,160 (23.3)	260 (25.2)	22.4	
80–84 years	1,144 (22.9)	222 (21.5)	19.4	
≥85 years	965 (19.4)	175 (16.9)	18.1	
Race/ethnicity				<.01
White, non-Hispanic	4,075 (81.7)	840 (81.3)	20.6	
African American	424 (8.5)	112 (10.8)	26.4	
White, Hispanic	232 (4.7)	51 (4.9)	22.0	
Other	254 (5.1)	30 (2.9)	11.8	
Male				.23
Yes	2,220 (44.5)	443 (42.9)	20.0	
No	2,765 (55.5)	590 (57.1)	21.3	
Married				.91
Yes	2,492 (50.0)	518 (50.2)	20.8	
No	2,493 (50.0)	515 (49.9)	20.7	
Poor performance status (proxy) ^{d,e}			0.03	
Yes	1,542 (30.9)	348 (33.7)	22.6	
No	3,443 (69.1)	685 (66.3)	19.9	
Charlson comorbidity index ^d				.03
0/unknown	2,730 (54.8)	536 (51.9)	19.6	
1	1,301 (26.1)	271 (26.2)	20.8	
≥2	954 (19.1)	226 (21.9)	23.7	
Substage of cancer ^f				.23
IIIA	552 (11.0)	113 (10.9)	20.5	
IIIB	2,939 (59.0)	588 (56.9)	20.0	
IIIC	1,494 (30.0)	332 (32.1)	22.2	
Chemotherapy receipt ^a				<.01
Yes	2,651 (53.2)	635 (61.5)	24.0	
No	2,334 (46.8)	398 (38.5)	17.1	

^aAny time during follow-up after cancer diagnosis.^bEquals the percentage of patients diagnosed with venous thromboembolism any time during follow-up.^cBased on Pearson χ^2 test of association, which tests for significant differences in rates of being diagnosed with venous thromboembolism any time during follow-up across patient categories.^dMeasured from claims in the year prior to cancer diagnosis.^eDefined as being hospitalized or having one or more claims for oxygen, walking aid, or wheelchair.^fCancer stage was derived by SEER in accordance with the 6th edition of the American Joint Committee on Cancer TNM system. More information can be found in Appendix C of the SEER Program Coding and Staging Manual 2004, Revision 1 (http://seer.cancer.gov/manuals/2004Revision%201/SPM_AppendixC_Part1_r1.pdf).

DISCUSSION

Colon cancer is the third most common cancer in men and women and the third leading cause of cancer deaths in the United States. Multiple factors independent of the T and N

staging that affect the survival of patients with colon cancer have been identified [32, 38]. VTE is the most common cause of 30-day mortality among patients with cancer undergoing surgery [21]. Furthermore, VTE remains the leading cause of

Table 2. Adjusted survival model for the hazard of death			
	Adjusted hazard ratio estimates	95% confidence interval	p-value
Venous thromboembolism diagnosis ^a	1.15	1.04–1.27	.01
Chemotherapy receipt ^a	0.39	0.36–0.43	<.01
Poor performance status (proxy) ^{b,c}	1.29	1.17–1.43	<.01
Charlson comorbidity index (vs. 0/unknown) ^b			
1	1.08	0.97–1.19	.16
≥2	1.29	1.15–1.45	<.01
Cancer substage (vs. substage IIIB) ^d			
IIIA	0.58	0.49–0.69	<.01
IIIC	1.72	1.57–1.88	<.01
Age (vs. 66–74 years)			
75–79 years	1.27	1.12–1.44	.00
80–84 years	1.34	1.19–1.52	<.01
≥85 years	1.60	1.40–1.82	<.01
Race/ethnicity (vs. non-Hispanic white)			
African American	1.09	0.94–1.27	.24
Hispanic white	1.09	0.90–1.33	.38
Other	0.78	0.63–0.97	.02
Male	1.15	1.06–1.26	.00
Married	0.88	0.80–0.96	.01

^aAny time during follow-up after cancer diagnosis.
^bMeasured from claims in the year prior to cancer diagnosis.
^cDefined as being hospitalized or having one or more claims for oxygen, walking aid, or wheelchair.
^dCancer stage was derived by SEER in accordance with the 6th edition of the American Joint Committee on Cancer TNM system. More information can be found in Appendix C of the SEER Program Coding and Staging Manual 2004, Revision 1 (http://seer.cancer.gov/manuals/2004Revision%201/SPM_AppendixC_Part1_r1.pdf).

Figure 1. Adjusted hazard ratio estimates for the effect of venous thromboembolism diagnosis on the hazard of death. Abbreviation: VTE, venous thromboembolism.

death in patients with overt malignancy, second only to the cancer diagnosis [20]. Prompt prevention, recognition, and management of VTE are becoming increasingly important for patients with colon cancer to avoid early death.

Our study of elderly patients with stage III colon cancer reports a 16% incidence rate of VTE in the year following cancer diagnosis. PE events occurred in 4.6% of patients, representing

28% of patients with VTE. Other studies have reported lower rates [4, 39]. The difference is attributable to four factors: (a) we focused only on patients with stage III colon cancer because of their unique clinical and treatment characteristics, including need for adjuvant chemotherapy, which puts them at higher risk for VTE; (b) we examined an elderly cohort; (c) VTE incidence was detected using primary and secondary di-

agnoses from both inpatient and outpatient claims; and (d) compared to clinical trials, which are more likely to enroll healthier patients, our real-world data represent the true population-based incidence.

Although the proportion of patients with VTE in the literature differs from our results, the association between VTE and mortality is consistent. Alcalay et al. previously reported 20% relative mortality hazards increase attributable to VTE within the first year of cancer diagnosis (CI: 10%–30%) [4]; Gross et al. reported a 19% increase in mortality hazards due to concomitant VTE, which was VTE diagnosed between 6 months before and 1 month after cancer diagnosis (CI: 6%–34%) [39]. This study provides additional evidence that clinically diagnosed VTE increases all-cause mortality. We estimated that elderly patients with stage III colon cancer who were diagnosed with VTE at any time during follow-up had 15% higher adjusted mortality hazards on average.

Adjuvant chemotherapy is considered standard treatment for patients with stage III colon cancer. However, some chemotherapy regimens increase the risk of VTE. It may be more clinically relevant to examine the impact of VTE on mortality separately among patients treated with chemotherapy, which is why stratified analyses were conducted. In our study, VTE was not associated with mortality in untreated patients after adjusting for covariates. Untreated patients in the current study were relatively older, had higher comorbidity burden, had worse performance status at baseline, and had significantly shorter survival, which might have led to underdetection or underreporting of VTE incidence.

Our results underscore the impact of VTE on mortality as a major public health problem and provide a reason for increased management and prevention of VTE among elderly patients with stage III colon cancer. Patients treated with chemotherapy may benefit the most from prophylactic antithrombotic treatment (Fig. 1). Other patients with a high risk of VTE may also benefit from anticoagulation prophylaxis [40]. It is noted, however, that VTE may reflect aggressive tumor biology, so the association of VTE and mortality is not always a direct effect.

The findings of this study should be considered in light of the following limitations. First, elderly patients with stage III colon cancer residing in the SEER geographic areas may differ compared with patients residing elsewhere in the United States. In addition, only VTE associated with healthcare utilization can be detected using claims data. VTE incidence may

have been overestimated due to ruling out VTE diagnoses. Also, the SEER registry does not report disease progression. Medicare Part D, which provides outpatient drug coverage for Medicare enrollees, did not start in the United States until 2006; therefore, Part D data was not available in the dataset, which means that information regarding prophylaxis and treatment for VTE was not available.

CONCLUSION

This study estimated a 15% increase in the hazard of death associated with clinically diagnosed VTE following stage III colon cancer diagnosis for elderly Medicare patients. This finding has implications for the assessment of VTE risk and prevention in patients with colon cancer beyond the critical care setting. For the subpopulation of patients treated with chemotherapy, VTE was associated with a mortality hazard increase of 41% (95% CI: 21%–64%), suggesting that the clinical presentation and management of VTE in this population may be more problematic given the proven survival advantage of adjuvant chemotherapy in patients with stage III colon cancer. These results provide further evidence that there may be additional survival benefit from greater prevention and management of VTE among patients with colon cancer who are treated with chemotherapy.

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This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors.

AUTHOR CONTRIBUTIONS

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